



HUMAN GENOME EPIDEMIOLOGY (HuGE) REVIEW

ERCC2/XPD Gene Polymorphisms and Lung Cancer: A HuGE Review

Simone Benhamou^{1,2} and Alain Sarasin²

¹ Institut National de la Santé et de la Recherche Médicale—Evry University, Evry, France.

² Centre National de la Recherche Scientifique, Unité Propre de Recherche 2169, Gustave-Roussy Institute, Villejuif, France.

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The xeroderma pigmentosum group D (XPD) protein is a well-characterized DNA helicase necessary for the nucleotide excision repair of bulky DNA lesions, such as those induced by cigarette smoking. Polymorphisms in several exons of the *XPD* gene have been identified; two of them, *Asp312Asn* and *Lys751Gln*, are common and result in an amino acid change. Most of the reported data indicate higher levels of DNA adducts in people carrying variant *Asn* or *Gln* alleles, which suggests that these persons have lower repair efficiency. These two polymorphisms have been hypothesized to modify the risk of lung cancer. To examine this association, the authors undertook a review and meta-analyses of nine published case-control studies. No clear association between *XPD Asp312Asn* or *XPD Lys751Gln* gene polymorphisms and lung cancer was found. However, it may be only the joint effect of multiple polymorphisms within the gene that provides information about an association with lung cancer. Because of advances in high-throughput genotyping techniques, it is likely that future association studies on lung cancer will need to investigate multiple polymorphisms within genes and multiple genes within the same pathway and will need to use recently developed haplotype-based methods to evaluate the haplotypic effects.

epidemiology; ERCC-2 protein; *ERCC2/XPD*; genetics; lung neoplasms; polymorphism (genetics); xeroderma pigmentosum

Abbreviations: ASR, world age-standardized rate per 100,000; CI, confidence interval; CYP, cytochrome P-450; EPHX, epoxide hydrolase; ERCC2, excision repair cross-complementing rodent repair deficiency, group 2; GST, glutathione *S*-transferase; MPO, myeloperoxidase; XPD, xeroderma pigmentosum group D; XRCC1, x-ray cross-complementing group 1.

Editor's note: This article is also available on the website of the Human Genome Epidemiology Network (<http://www.cdc.gov/genomics/hugenet/default.htm>).

GENE

The excision repair cross-complementing rodent repair deficiency, group 2 (*ERCC2*) gene, also called the xero-

derma pigmentosum group D (*XPD*) gene, is located at chromosome 19q13.3. It comprises 23 exons and spans about 54,000 base pairs (1). The cDNA is unique, with a size of 2,400 nucleotides. The *XPD* gene product is a protein of 760 amino acids with a molecular weight of 86,900 and adenosine triphosphate-dependent 5'–3' DNA helicase activity. The XPD protein is a component of the core transcription factor IIIH, which is involved in nucleotide excision repair of DNA by opening DNA around the

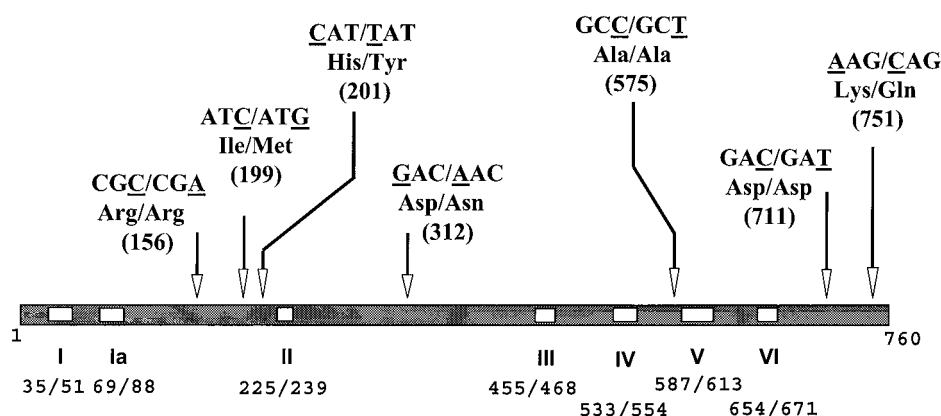


FIGURE 1. Locations of various polymorphisms on the excision repair cross-complementing rodent repair deficiency, group 2/xeroderma pigmentosum group D (*XPB*) gene. The *XPB* protein is composed of 760 amino acids. The open rectangles demarcated by the numbered amino acids correspond to the consensus domains for DNA-DNA helicase activity (Roman numerals). The codon numbers and eventual amino acid changes for the seven polymorphisms studied in this paper are indicated, according to the work of Shen et al. (7) and Mohrenweiser et al. (8).

damage (2). It also acts in the initiation of RNA transcription by RNA polymerase II by anchoring the cyclin-dependent kinase-activating kinase complex, which is composed of cyclin-dependent kinase 7 (*cdk7*), cyclin H, and ménage à trois 1 (*MAT1*), to the core transcription factor IIH complex (3).

Nucleotide excision repair is the major pathway for removal of bulky DNA lesions, particularly those induced by cigarette smoking. The *XPB* protein is absolutely necessary in nucleotide excision repair. Once the DNA lesion has been recognized by specific proteins, the helicase activity of *XPB*, in concerted action with the xeroderma pigmentosum group

TABLE 1. Phenotypic endpoints relevant for lung carcinogenesis associated with *ERCC2**/*XPB**-312 and -751 gene polymorphisms

Phenotypic endpoints	Population studied	Codon	Results	Study authors and year (ref. no.)
Polyphenol DNA adducts in blood mononuclear cells by ³² P-postlabeling	61 friends or spouses of lung cancer cases	751	No correlation between the polymorphism and levels of DNA adducts	Duell et al., 2000 (9)
³² P-postlabeling in leukocyte DNA	114 workers exposed to traffic pollution	751	Higher mean levels of DNA adducts with at least one <i>Gln</i> allele	Palli et al., 2001 (10)
Host-cell reactivation of the <i>CAT</i> * gene in BPDE*-treated plasmid transfected in blood cells	341 lung cancer cases and 360 controls	312	Trend of lower repair by increasing number of <i>Asn</i> alleles in cases†	Spitz et al., 2001 (11)
		751	Trend of lower repair by increasing number of <i>Gln</i> alleles in cases†	
Aromatic DNA adducts measured by thin-layer chromatography in lymphocytes	185 lung cancer cases and 162 controls	312	Trend of increasing adduct levels with increasing number of <i>Asn</i> alleles‡	Hou et al., 2002 (12)
		751	Trend of increasing adduct levels with increasing number of <i>Gln</i> alleles‡	
Host-cell reactivation of a reporter gene in ultraviolet light-treated plasmid transfected in blood lymphocytes	102 healthy non-Hispanic White subjects	312	Lower repair activity for the <i>Asn/Asn</i> genotype versus the other genotypes§	Qiao et al., 2002 (13)
		751	Lower repair activity for the <i>Gln/Gln</i> genotype versus the other genotypes§	
Polycyclic aromatic hydrocarbon-DNA adducts measured by immunohistochemistry in breast tissue	103 breast cancer cases and 121 controls	312	Higher adduct levels with the <i>Asp/Asn</i> or <i>Asn/Asn</i> genotype versus the <i>Asp/Asp</i> genotype in breast tumor tissue	Tang et al., 2002 (14)
		751	Increased adduct levels in breast tumor tissue with increasing number of <i>Gln</i> alleles	
DNA adducts in white blood cells by ³² P-postlabeling	628 healthy Italians	751	Higher level of adducts in nonsmokers with the <i>Gln/Gln</i> genotype	Matullo et al., 2003 (15)

* ERCC2, excision repair cross-complementing rodent repair deficiency, group 2; *XPB*, xeroderma pigmentosum group D; *CAT*, chloramphenicol acetyltransferase; BPDE, benzo(a)pyrene diol epoxide.

† Persons who were homozygous for wild-type alleles at both loci exhibited the best repair level. Trend test: $p = 0.001$ for cases.

‡ There was a higher adduct level for the *Asn312Asn* and *Gln751Gln* genotypes than for all other genotypes.

§ The lowest DNA repair capacity was associated with the highest number of homozygous variant genotypes ($p = 0.02$).

TABLE 2. Frequencies of the ERCC2*/XPD* Arg156Arg gene polymorphism, by geographic region

Study authors and year (ref. no.)	Country	Population studied	Ethnicity	Hardy-Weinberg <i>p</i> value	Total no. of subjects	Genotype frequency (%)			Frequency (%) of the A allele	95% confidence interval
						CC	CA	AA		
Europe										
Winsey et al., 2000 (16)†	United Kingdom	Cadaveric renal transplant donors	Caucasian	ND*,‡	211	33	54	13	40	ND‡
North America										
Sturgis et al., 2000 (17)†	United States	Hospital	Non-Hispanic White	0.70	496	31.0	48.6	20.4	45	42, 48
Vogel et al., 2001 (18)†	United States	Hospital	Caucasian	0.19	111	37.8	42.3	19.8	41	35, 47
Caggana et al., 2001 (19)†	United States	Population	Caucasian	0.28	139	39.6	43.2	17.3	39	33, 45
Qiao et al., 2002 (20)†	United States	Visitors/companions of cancer patients	Non-Hispanic White	0.42	102	24.5	53.9	21.6	49	42, 55

* ERCC2, excision repair cross-complementing rodent repair deficiency, group 2; XPD, xeroderma pigmentosum group D; ND, not determined.

† Case-control study. Only frequencies for the control group are included in the table.

‡ Not determined because numbers of subjects by genotype were not provided in the published article.

B helicase, allows the opening of the double helix so that the damaged strand can be cut and the damaged piece of DNA removed. A similar helix opening activity allows the initiation of RNA transcription by RNA polymerase II. XPD activity is essential for life; total absence of the *XPD* gene results in embryonic lethality (4).

Point mutations in the human XPD protein play a causative role in DNA repair-deficiency diseases (xeroderma pigmentosum, trichothiodystrophy, and Cockayne syndrome), which are characterized by high ultraviolet-light hypersensitivity, a high mutation frequency, and cancer-proneness, as well as some mental and growth retardation and probably aging (5). Most of these mutations are located in the C-terminal part of the protein, which is the domain of interaction, inside the transcription factor IIH complex, with the p44 protein being necessary for activating the helicase activity (3). The very high cancer-proneness of xeroderma pigmentosum patients (including internal cancers) shows clearly the relevant association between DNA repair efficiency and cancer risk.

GENE VARIANTS

Because the XPD protein is absolutely necessary for efficient nucleotide excision repair, DNA repair-deficient cells arising from a mutation in the *XPD* gene exhibit low unscheduled DNA synthesis and low survival following ultraviolet irradiation. However, these two biologic assays are not sensitive enough to detect small DNA-repair defects, as might be expected from polymorphisms in DNA repair genes. Most investigations of the effect of *XPD* polymorphisms on cell repair capability have used the host cell reactivation assay, wherein a reporter gene present in a damaged plasmid (a plasmid treated with ultraviolet light or benzo(a)pyrene diol epoxide) is transfected into human cells for quantification of the level of DNA repair. This technique is one of the most sensitive ones but until now has measured the repair level of blood lymphocytes that are not the target cells for carcinogenesis. The measure of DNA adducts can

also quantify the DNA repair level of cells treated in vitro by a given genotoxic agent or can determine a steady-state amount in lymphocytes from individuals between the level of exposure and the level of repair. These experiments have utilized several assays to quantify the number of DNA lesions, such as ³²P-postlabeling, immunohistochemistry, or thin-layer chromatography. Other phenotypic effects have been evaluated, but because they are not directly interpretable for lung carcinogenesis, we do not describe them in this review.

Besides point mutations that cause diseases and are found in the homozygous state in patients or on only one *XPD* allele in asymptomatic parents, seven polymorphisms in exons 6, 8, 10, 17, 22, and 23 of the *XPD* gene have been identified by sequencing the DNA of individuals (6–8). Three of these polymorphisms are silent, and the remaining four result in amino acid changes (figure 1). Whereas the codon 199, codon 201, and codon 575 polymorphisms are rare (allele frequency ~1 percent), those in codons 156, 312, 711, and 751 are common (allele frequencies >25 percent) (7, 8). Two *XPD* polymorphisms (i.e., *Asp312Asn* and *Lys751Gln*) have mainly been investigated in relation to phenotypic endpoints relevant to lung carcinogenesis (9–15; table 1). Concerning the *Asp312Asn* polymorphism, most of the reported data indicate a higher level of DNA adducts in *Asn* individuals than in *Asp* individuals, which is interpreted as a lower repair efficiency for the *XPD Asn* allele. This is also true for the *Lys751Gln* polymorphism; the *Gln* allele is associated with a higher DNA adduct level or lower DNA repair efficiency, except in research by Duell et al. (9), who found no correlation between the *XPD*-751 polymorphism and the level of polyphenol–DNA adducts in human blood samples. Matullo et al. (15) demonstrated a higher level of DNA adducts, measured by ³²P-postlabeling, in lymphocytes from nonsmokers with the *XPD*-751 *Gln* homozygous genotype. Similarly, Palli et al. (10) reported a higher level of DNA adducts in workers with at least one *Gln* allele who were exposed to traffic pollution in comparison with workers with the two common alleles. Levels of polycyclic aromatic

TABLE 3. Frequencies of the *ERCC2**/*XPD** *Asp312Asn* gene polymorphism, by geographic region

Study authors and year (ref. no.)	Country	Population studied	Ethnicity	Hardy-Weinberg <i>p</i> value	Total no. of subjects	Genotype frequency (%)			Frequency (%) of the <i>Asn</i> allele	95% confidence interval
						<i>Asp/Asp</i>	<i>Asp/Asn</i>	<i>Asn/Asn</i>		
<i>Asia</i>										
Liang et al., 2003 (21)†	China	Population	Chinese	0.09	1,020	87.2	12.7	0.1	6	5, 8
<i>Europe</i>										
Misra et al., 2003 (22)†	Finland	Population, male smokers	Not specified	0.75	312	40.1	47.1	12.8	36	33, 40
Winsey et al., 2000 (16)†	United Kingdom	Cadaveric renal transplant donors	Caucasian	ND*,‡	211	42	45	13	36	ND‡
Hou et al., 2002 (12)†	Sweden	Population	Not specified	0.55	162	40.7	44.4	14.8	37	32, 42
<i>North America</i>										
Zhou et al., 2002 (23)†	United States	Friends/nonblood relatives of cancer patients	Caucasian	0.15	1,240	43.8	46.1	10.1	33	31, 35
Vogel et al., 2001 (18)†	United States	Hospital patients	Caucasian	0.04	105	43.8	37.1	19.1	38	31, 44
Caggana et al., 2001 (19)†	United States	Population	Caucasian	0.85	137	40.9	46.7	12.4	36	30, 41
Sturgis et al., 2002 (24)†	United States	Hospital patients	Non-Hispanic White	0.65	313	45.4	43.1	11.5	33	29, 37
Qiao et al., 2002 (20)	United States	Visitors/companions of cancer patients	Non-Hispanic White	0.30	102	52.0	37.3	10.8	29	23, 36

* *ERCC2*, excision repair cross-complementing rodent repair deficiency, group 2; *XPD*, xeroderma pigmentosum group D; ND, not determined.

† Case-control study. Only frequencies for the control group are included in the table.

‡ Not determined because numbers of subjects by genotype were not provided in the published article.

hydrocarbon–DNA adducts were higher in breast cancer tissue in patients with at least one 312 *Asn* allele or one 751 *Gln* allele (14). An increased number of aromatic DNA adducts has been found by Hou et al. (12) in peripheral blood lymphocytes from persons with *XPD*-312 and -751 variant alleles. The combined variant genotypes showed a higher level of DNA lesions than did other genotypes. This generally higher level of DNA adducts associated with variant alleles is in agreement with the lower DNA repair demonstrated by means of the host cell reactivation technique. Spitz et al. (11) reported that *Asn312Asn* and *Gln751Gln* genotypes were significantly associated with lower DNA repair of plasmid treated with benzo(*a*)pyrene diol epoxide. Similar results were obtained by Qiao et al. (13) using an ultraviolet light-damaged plasmid.

Following the study by Shen et al. (7), three *XPD* polymorphisms, *Arg156Arg*, *Asp312Asn*, and *Lys751Gln*, were mainly investigated in genetic epidemiologic studies because of their high frequencies and/or amino acid substitution variants. In this review, we focus on the prevalence of these polymorphisms in different populations and their potential effect on lung cancer risk.

We conducted a MEDLINE search using “*ERCC2*” or “*XPD*” and “polymorphism” for papers published before December 2003. The search was limited to human subjects, without language restriction. For case-control studies, only genotype frequencies for the control population were considered. Studies that reported only allele frequencies and no genotype frequencies were not included. Studies based on fewer than 100 persons were excluded. When a subset of the

same control population was used in several publications, we retained the results based on the largest sample size. For each study, we assessed the Hardy-Weinberg equilibrium via a goodness-of-fit χ^2 test to compare the observed and expected genotype frequencies.

We identified 18 publications reporting on the prevalence of *XPD* polymorphisms (11, 12, 15–30). Genotype frequencies were in agreement with those predicted under the conditions of Hardy-Weinberg equilibrium in almost all populations (tables 2, 3, and 4). Fewer than half of the studies were population based, and except for two large studies based on more than 1,000 persons, most of the remaining studies had sample sizes in the range of 100–300. These differences in study design could make it difficult to determine the extent to which apparent geographic or ethnic variation reflects genetic differences or methodological factors.

The genotype frequencies of the *XPD Arg156Arg* polymorphism are shown in table 2. Neither the *C* allele nor the *A* allele was predominant in the four studies carried out in the United States; approximately half of the persons studied had the heterozygous *C/A* genotype and 20 percent carried the homozygous *A/A* genotype. In the United Kingdom, a lower frequency of the *A/A* genotype (13 percent) was reported among cadaveric renal transplant donors; however, we were unable to test for Hardy-Weinberg equilibrium in this population, because the genotype distribution was not provided in the published article (16). No information on other geographic regions was available.

TABLE 4. Frequencies of the ERCC2*/XPD* Lys751Gln gene polymorphism, by geographic region

Study authors and year (ref. no.)	Country	Population studied	Ethnicity	Hardy-Weinberg <i>p</i> value	Total no. of subjects	Genotype frequency (%)			Frequency (%) of the <i>Gln</i> allele	95% confidence interval
						<i>Lys/Lys</i>	<i>Lys/Gln</i>	<i>Gln/Gln</i>		
<i>Asia</i>										
Chen et al., 2002 (25)†	China	Community centers/ cancer screening programs	Chinese	0.37	109	37.6	44.0	18.4	40	34, 47
Liang et al., 2003 (21)†	China	Population	Chinese	0.49	1,020	83.1	16.3	0.6	9	8, 10
Park et al., 2002 (26)†	South Korea	Males, health center visitors	Korean	ND*,‡	163	89.0	11.0	0.0	6	ND
Hamajima et al., 2002 (27)	Japan	Hospital	Japanese	0.08	240	90.4	8.8	0.8	5	3, 7
<i>Europe</i>										
Misra et al., 2003 (22)	Finland	Population, male smokers	Not specified	0.38	302	34.1	50.7	15.2	41	37, 44
Shen et al., 2003 (28)	Italy	Hospital, males	Caucasian	0.52	214	37.4	45.8	16.8	40	35, 44
Matullo et al., 2003 (15)	Italy	Population	Not specified	ND‡	628	34.3	50.7	15.0	40	ND‡
Hou et al., 2002 (12)	Sweden	Population	Not specified	0.07	162	42.6	40.1	17.3	37	32, 43
Winsey et al., 2000 (16)	United Kingdom	Cadaveric transplant donors	Caucasian	ND‡	211	34	51	15	40	ND‡
<i>North America</i>										
David-Beabes et al., 2001 (29)†	United States	Population	African-American	0.57	234	55.6	38.9	5.6	25	21, 29
David-Beabes et al., 2001 (29)†	United States	Population	Caucasian	0.46	453	43.5	43.7	12.8	35	32, 38
Zhou et al., 2002 (23)†	United States	Friends/nonblood relatives of cancer patients	Caucasian	0.99	1,240	40.2	46.4	13.4	37	35, 38
Vogel et al., 2001 (18)†	United States	Hospital patients	Caucasian	0.17	117	37.6	52.1	10.3	36	30, 42
Spitz et al., 2001 (11)†	United States	Hospital patients	Caucasian	0.81	360	44.2	45.0	10.8	33	30, 37
Stern et al., 2002 (30)†	United States	Hospital patients	Caucasian	0.50	197	40.1	44.7	15.2	38	33, 42
Caggana et al., 2001 (19)†	United States	Population	Caucasian	0.47	148	33.1	51.4	15.5	41	36, 47
Qiao et al., 2002 (20)	United States	Visitors/companions of cancer patients	Non-Hispanic White	0.05	102	45.1	37.3	17.7	36	30, 43

* ERCC2, excision repair cross-complementing rodent repair deficiency, group 2; XPD, xeroderma pigmentosum group D; ND, not determined.

† Case-control study. Only frequencies for the control group are included in the table.

‡ Not determined because numbers of subjects by genotype were not provided in the published article.

Table 3 shows the genotype frequencies for the XPD Asp312Asn polymorphism. The Asn allele was frequently observed in Europe and the United States, typically with 40–50 percent Asp/Asn heterozygosity and 10–15 percent Asn/Asn homozygosity. In contrast, the Asn allele was uncommon in the one large Chinese study (21), and Asn/Asn homozygosity was rarely reported.

With regard to the XPD Lys751Gln polymorphism (table 4), the Gln allele was common in Europe and North America; approximately 50 percent of these persons carried the heterozygous Lys/Gln genotype and 10–15 percent had the homozygous Gln/Gln genotype. The Gln allele was less frequently reported in African Americans, with 5.6 percent Gln/Gln homozygosity (29). This allele was uncommon in

China (21), South Korea (26), and Japan (27): Nearly 90 percent of the subjects carried the Lys/Lys genotype, and the Gln/Gln genotype was rarely observed. However, this pattern of genotype frequencies was very different in another Chinese population (25), with approximately 18 percent of subjects carrying the homozygous Gln/Gln genotype. Errors in genotyping might explain these discrepant results, since it seems unlikely that such great variation would exist in a population where all persons were of the same ethnicity.

DISEASE

Lung cancer is the most common malignant disease worldwide; 900,000 new cases are diagnosed each year in men and

TABLE 5. Description of case-control studies on *ERCC2/*XPD** gene polymorphisms and lung cancer risk**

Study authors and year (ref. no.)	Country	Description of cases	No. of subjects	Description of controls	No. of subjects	Matching criteria
Butkiewicz et al., 2001 (48)	Poland	Histologically confirmed non-small-cell lung cancer; 100% males; 82% ever smokers	96	Subjects recruited for previous occupational studies; 100% males; 82% ever smokers	96	Age, smoking status, and occupational exposure
David-Beabes et al., 2001 (29)	United States	Incident; histologically confirmed; ages 40–84 years; 58% males; 96% ever smokers	331	Population controls; all residents of Los Angeles County, California; ages 40–84 years; 67% males; 66% ever smokers	687	Age, sex, and ethnicity
Spitz et al., 2001 (11)	United States	Incident; histologically confirmed; 100% Whites; 50% males; 90% ever smokers	341	Hospital controls recruited from a managed-care organization; 100% Whites; 55% males; 91% ever smokers	360	Age, sex, and smoking status
Chen et al., 2002 (25)	China	Incident; histologically confirmed; 83% males; 72% ever smokers	109	Volunteers from community centers and cancer screening programs; 83% males; 70% ever smokers	109	Age, sex, and smoking status
Hou et al., 2002 (12)	Sweden	Incident; histologically confirmed; 25% males; 52% ever smokers	185	Population controls; persons extracted from Stockholm residence files; 29% males; 51% ever smokers	162	Hospital catchment area, age, gender, and smoking status
Park et al., 2002 (26)	South Korea	Histologically confirmed; 100% males; percentage of ever smokers not precise	250	Volunteers from a general health check-up center; 100% males; percentage of ever smokers not precise	163	Age
Zhou et al., 2002 (23)	United States	Incident; histologically confirmed; 54% males; 93% ever smokers	1,092	Friends and nonblood relatives of cases; 46% males; 65% ever smokers	1,240	None
Liang et al., 2003 (21)	China	Incident; histologically confirmed; 73% males; 66% ever smokers	1,006	Subjects randomly selected from a pool of cancer-free patients recruited from a nutritional survey; 72% males; 49% ever smokers	1,020	Age and sex
Misra et al., 2003 (22)	Finland	Incident; 100% males; 100% ever smokers	315	Cancer-free participants in the ATBC* Cancer Prevention Study; 100% males; 100% ever smokers	315	Age, intervention group, study clinic, and date of blood drawing

* ERCC2, excision repair cross-complementing rodent repair deficiency, group 2; XPD, xeroderma pigmentosum group D; ATBC, Alpha-Tocopherol, Beta-Carotene.

330,000 in women (31). It is the leading cause of death from cancer. It accounts for 12.3 percent of all incident cancers and 17.8 percent of cancer deaths (31). Lung cancer incidence varies markedly throughout the world (32). In men, the incidence rate (world age-standardized rate per 100,000 (ASR)), including all histologic types, varies up to 35-fold between high- and low-risk areas. The highest rates are recorded among Blacks in the United States (New Orleans, Louisiana: ASR = 107; Detroit, Michigan: ASR = 95) and in Lower Silesia, Poland (ASR = 92), while the lowest rates are recorded in Africa (Bamako, Mali: ASR = 3; Kyadondo, Uganda: ASR = 4; The Gambia: ASR = 5). For women, lung cancer incidence rates are below 1 in Africa (Bamako, Mali: ASR = 0.1; The Gambia: ASR = 0.6) and less than 45 in all populations, except the Northwest Territories of Canada (ASR = 72). Males consistently show a higher incidence than do females in all populations, with male:female ratios varying approximately from 1.5 to 20 (32). Both geographic and gender disparities are mainly due to differences in patterns of tobacco smoking.

Smoking is the main risk factor for lung cancer, accounting for approximately 90 percent of cases in men in industrialized countries (33). Smoking induces lung cancer of all of the major histologic types; the strongest association

has been reported for squamous cell carcinoma (34), which is the most common type of lung cancer in many populations. Male smokers have 8–15 times the lung cancer risk of nonsmokers (31). Dose-response relations have been observed for both intensity of smoking (i.e., daily tobacco consumption) and duration of smoking (33). In addition, there is evidence for an association between exposure to secondhand smoke and lung cancer risk in nonsmokers (35); systematic reviews have identified an excess risk on the order of 25 percent in nonsmokers who have ever lived with a smoker (36, 37), and clear dose-response relations between exposure to secondhand smoke from different sources and the development of lung cancer among never smokers were recently reported (38).

An increased risk of lung cancer has been established for employment in several industries and for domestic radon exposure (International Agency for Research on Cancer monographs, 1972–2001 (<http://monographs.iarc.fr>)). There are also consistent results on inverse associations between fruit and vegetable consumption and lung cancer risk (39).

Many xenobiotic metabolizing enzymes, such as cytochrome P-450 (CYP), glutathione *S*-transferase (GST), epoxide hydrolase (EPHX), and myeloperoxidase (MPO), are involved in the metabolism of carcinogenic polycyclic

TABLE 6. Findings from published studies on the association between the *ERCC2/*XPD** *Asp312Asn* gene polymorphism and lung cancer risk and the interaction of the polymorphism with smoking**

Study authors and year (ref. no.)	Total no. of cases	Total no. of controls	Genotype	No. of cases	No. of controls	OR*	95% CI*	Gene × smoking interaction
Butkiewicz et al., 2001 (48)	96	94	<i>Asp/Asp</i>	43	29	1†		Decreased risk for <i>Asn/Asn</i> genotype in light smokers (<34.5 pack-years)‡
			<i>Asp/Asn</i>	35	48	0.5§	0.2, 1.0§	
			<i>Asn/Asn</i>	18	17	0.7§	0.3, 1.7§	
Spitz et al., 2001 (11)	195	257	<i>Asp/Asp</i>	102	135	1†		Not studied
			<i>Asp/Asn</i>	72	104	0.9¶	0.6, 1.4	
			<i>Asn/Asn</i>	21	18	1.5¶	0.8, 3.0	
Hou et al., 2002 (12)	184	162	<i>Asp/Asp</i>	68	66	1†		Increased risk in never smokers with the <i>Asn</i> allele (OR = 1.8, 95% CI: 0.9, 3.3)#
			<i>Asp/Asn</i>	94	72	1.3§	0.8, 2.1§	
			<i>Asn/Asn</i>	22	24	0.9§	0.4, 1.8§	
Zhou et al., 2002 (23)	1,092	1,240	<i>Asp/Asp</i>	463	543	1†		Increased risk in never smokers with the <i>Asn/Asn</i> genotype (OR = 4.4, 95% CI: 2.2, 9.2)**
			<i>Asp/Asn</i>	479	572	1.0††	0.8, 1.2	
			<i>Asn/Asn</i>	150	125	1.5††	1.1, 2.0	
Liang et al., 2003 (21)	1,006	1,020	<i>Asp/Asp</i>	870	889	1†		Not studied
			<i>Asp/Asn</i>	125	130	1.0¶	0.8, 1.4	
			<i>Asn/Asn</i>	11	1	10.3¶	1.3, 82.5	
Misra et al., 2003 (22)	313	312	<i>Asp/Asp</i>	143	125	1†		No significant interaction‡
			<i>Asp/Asn</i>	127	147	0.7‡‡	0.5, 1.0	
			<i>Asn/Asn</i>	43	40	0.9‡‡	0.6, 1.6	

* ERCC2, excision repair cross-complementing rodent repair deficiency, group 2; XPD, xeroderma pigmentosum group D; OR, odds ratio; CI, confidence interval.

† Reference category.

‡ Reported in the published article.

§ Crude OR and 95% CI (Cornfield's method) calculated using published data.

¶ Adjusted for sex, age, and smoking status.

Adjusted for sex, age, and environmental tobacco smoke exposure.

** Adjusted for sex and age.

†† Adjusted for sex, age, square root of pack-years of smoking, and years since cessation of smoking.

‡‡ Adjusted for sex, age, smoking status, and pack-years of smoking.

aromatic hydrocarbons contained in tobacco smoke. Several polymorphisms in genes encoding these enzymes have been examined in relation to lung cancer in numerous studies; this part of the review is restricted to summarized results provided by recent meta- and pooled analyses. Two polymorphisms in the *CYP1A1* gene, a T3801C substitution at the 3' end of the gene and an A2455G substitution resulting in an *Ile462Val* exchange in the heme-binding region of exon 7, appear to increase lung cancer risk in Caucasians (40–42). The *CYP1A1 Ile462Val* polymorphism might also play a role in lung carcinogenesis among nonsmokers (43). A slight excess risk of lung cancer among carriers of the *GSTM1* null genotype (44) or the *GSTP1**B/*B genotype (45) has also been suggested. In addition, there is some evidence for a protective effect of a polymorphism in the promoter region of the *MPO* gene (46) and in exon 3 of the *EPHX* gene (47). No associations have been observed for the *GSTT1* null genotype in Caucasians (41).

ASSOCIATIONS AND INTERACTIONS

To our knowledge, nine case-control studies have investigated the associations of *Asp312Asn* and/or *Lys751Gln* poly-

morphisms with lung cancer risk (11, 12, 21–23, 25, 26, 29, 48). The designs and main results of these studies are summarized in tables 5, 6, and 7. Except for two large studies based on more than 1,000 cases and a similar number of controls, the studies contained approximately 100–300 cases each. All of the studies were conducted with incident cases, but only two of them used population-based controls. A protective effect of the *XPD*-312 *Asn* allele was suggested in one study based on a small sample size (48). In contrast, the *Asn/Asn* homozygous genotype was associated with increased risk of lung cancer in the two largest studies (21, 23; table 6); however, the findings of one of these studies were based on 11 cases and one control (21). No clear association between the *Asn* allele and lung cancer risk was found in the remaining studies. Regarding the *Lys751Gln* polymorphism (table 7), no significant increased risk of lung cancer was observed overall for possession of the *Lys/Gln* heterozygous genotype or the *Gln/Gln* homozygous genotype. A 2.7-fold risk associated with the *Gln/Gln* genotype was suggested in one study (21), but this result was based on small numbers of subjects (14 cases and six controls).

We undertook meta-analyses of these studies. We had a total of 2,886 cases and 3,085 controls for the *XPD*-312

TABLE 7. Findings from published studies on the association between the *ERCC2/*XPD** *Lys751 Gln* gene polymorphism and lung cancer risk and the interaction of the polymorphism with smoking**

Study authors and year (ref. no.)	Total no. of cases	Total no. of controls	Genotype	No. of cases	No. of controls	OR*	95% CI*	Gene × smoking interaction
Butkiewicz et al., 2001 (48)	96	96	<i>Lys751 Gln</i>	Not given		No association†		Not studied
David-Beabes et al., 2001 (29)	331	687	<i>Lys/Lys</i>	146	327	1‡		No significant interaction†
			<i>Lys/Gln</i>	140	289	1.0§	0.7, 1.4	
			<i>Gln/Gln</i>	45	71	1.3§	0.8, 2.2	
Spitz et al., 2001 (11)	341	360	<i>Lys/Lys</i>	141	159	1‡		Not studied
			<i>Lys/Gln</i>	153	162	1.1¶	0.8, 1.5	
			<i>Gln/Gln</i>	47	39	1.4¶	0.8, 2.2	
Chen et al., 2002 (25)	109	109	<i>Lys/Lys</i>	51	41	1‡		No significant interaction†
			<i>Lys/Gln</i>	47	48	0.8#	0.4, 1.5#	
			<i>Gln/Gln</i>	11	20	0.4#	0.2, 1.1#	
Hou et al., 2002 (12)	185	162	<i>Lys/Lys</i>	71	69	1‡		Increased risk in never smokers with the <i>Gln</i> allele (OR = 2.0, 95% CI: 1.1, 3.8)**
			<i>Lys/Gln</i>	82	65	1.2#	0.8, 2.0#	
			<i>Gln/Gln</i>	32	28	1.1#	0.6, 2.1#	
Park et al., 2002 (26)	250	163	<i>Lys751 Gln</i>	Not given		No association†		Not studied
Zhou et al., 2002 (23)	1,092	1,240	<i>Lys/Lys</i>	428	499	1‡		Increased risk in never smokers with the <i>Gln/Gln</i> genotype (OR = 2.1, 95% CI: 1.0, 4.2)††
			<i>Lys/Gln</i>	498	575	1.0‡‡	0.8, 1.2	
			<i>Gln/Gln</i>	166	166	1.1‡‡	0.8, 1.4	
Liang et al., 2003 (21)	1,006	1,020	<i>Lys/Lys</i>	839	848	1‡		Not studied
			<i>Lys/Gln</i>	153	166	1.0§§	0.7, 1.2	
			<i>Gln/Gln</i>	14	6	2.7§§	1.0, 7.2	
Misra et al., 2003 (22)	310	302	<i>Lys/Lys</i>	112	103	1‡		No significant interaction†
			<i>Lys/Gln</i>	145	153	0.8§§	0.6, 1.2	
			<i>Gln/Gln</i>	53	46	1.0§§	0.6, 1.7	

* *ERCC2*, excision repair cross-complementing rodent repair deficiency, group 2; *XPD*, xeroderma pigmentosum group D; OR, odds ratio; CI, confidence interval.

† Reported in the publication. ORs and 95% CIs were not calculated because the genotype distribution was not given in the published article.

‡ Reference category.

§ Adjusted for age and smoking.

¶ Adjusted for sex, age, and smoking status.

Crude OR and 95% CI (Cornfield's method) calculated using published data.

** Adjusted for sex, age, and environmental tobacco smoke exposure.

†† Adjusted for sex and age.

‡‡ Adjusted for sex, age, square root of pack-years of smoking, and years since cessation of smoking.

§§ Adjusted for sex, age, smoking status, and pack-years of smoking.

polymorphism (six studies) and 3,374 cases and 3,880 controls for the *XPD*-751 polymorphism (seven studies; two studies were not included because genotype distributions were not provided in the published articles (26, 48)). Random-effects models were fitted. The homogeneity of the study results was assessed via the *Q* statistic, with *p* values less than 0.05 indicating a lack of homogeneity (49). Summary odds ratios were calculated for all of the studies combined, as well as by geographic region (Asia, Europe, and North America) when possible. Meta-analysis of data from published reports can produce biased results if the included studies are a biased sample of studies in general (50); therefore, we assessed publication bias using the test of Egger et al. (51).

Summary odds ratios associated with the *XPD*-312 gene polymorphism are shown in table 8 and figures 2 and 3. No significant association between lung cancer and the heterozygous *Asp/Asn* genotype was found for all of the studies combined or by geographic region. A summary odds ratio of 1.18 (95 percent confidence interval (CI): 0.84, 1.67) was found for carriers of the *XPD*-312 *Asn/Asn* genotype. Statistical tests indicated no significant heterogeneity of individual study results (*p* value for *Q* statistic = 0.09). Grouping results by geographic region revealed a significantly increased risk of lung cancer associated with the homozygous variant genotype in the United States only (odds ratio = 1.43, 95 percent CI: 1.11, 1.83). This finding was entirely due to the study by Zhou et al. (23), which is

TABLE 8. Odds ratios for the association of *ERCC2/*XPD**-312 and -751 gene polymorphisms with lung cancer in a meta-analysis**

Polymorphism and geographic region	Total no. of cases	Total no. of controls	Genotype	No. of cases	%	No. of controls	%	Odds ratio	95% confidence interval	<i>p</i> value for <i>Q</i> statistic
<i>Asp312Asn gene polymorphism</i>										
All studies	2,886	3,085	<i>Asp/Asp</i>	1,689	59	1,787	64	1†		
			<i>Asp/Asn</i>	932	32	1,073	35	0.92	0.78, 1.08	0.18
			<i>Asn/Asn</i>	265	9	225	7	1.18	0.84, 1.67	0.09
Europe	593	568	<i>Asp/Asp</i>	254	43	220	39	1†		
			<i>Asp/Asn</i>	256	43	267	47	0.81	0.50, 1.29	0.05
			<i>Asn/Asn</i>	83	14	81	14	0.88	0.61, 1.25	0.85
United States	1,287	1,497	<i>Asp/Asp</i>	565	52	678	45	1†		
			<i>Asp/Asn</i>	551	43	676	45	0.97	0.83, 1.14	0.75
			<i>Asn/Asn</i>	171	13	143	10	1.43	1.11, 1.83	0.80
<i>Lys751Gln gene polymorphism</i>										
All studies	3,374	3,880	<i>Lys/Lys</i>	1,788	53	2,046	53	1†		
			<i>Lys/Gln</i>	1,218	36	1,458	38	1.00	0.90, 1.11	0.83
			<i>Gln/Gln</i>	368	11	376	10	1.18	0.95, 1.47	0.20
Asia	1,115	1,129	<i>Lys/Lys</i>	890	80	889	79	1†		
			<i>Lys/Gln</i>	200	18	214	19	0.91	0.73, 1.13	0.60
			<i>Gln/Gln</i>	25	2	26	2	1.00	0.20, 5.18	0.01
Europe	495	464	<i>Lys/Lys</i>	183	37	172	37	1†		
			<i>Lys/Gln</i>	227	46	218	47	1.00	0.72, 1.38	0.25
			<i>Gln/Gln</i>	85	17	74	16	1.08	0.74, 1.57	0.91
United States	1,764	2,287	<i>Lys/Lys</i>	715	41	985	43	1†		
			<i>Lys/Gln</i>	791	45	1,026	45	1.04	0.91, 1.19	0.90
			<i>Gln/Gln</i>	258	15	276	12	1.25	1.03, 1.52	0.68

* ERCC2, excision repair cross-complementing rodent repair deficiency, group 2; XPD, xeroderma pigmentosum group D.

† Reference category.

consistent with the larger study size and the significant result observed (odds ratio = 1.5, 95 percent CI: 1.1, 2.0). There was no evidence of a relation in Europe (odds ratio = 0.88, 95 percent CI: 0.61, 1.25). With regard to the *XPD*-751 gene polymorphism, inclusion of all studies produced a summary odds ratio of 1.00 (95 percent CI: 0.90, 1.11) for heterozygotes and 1.18 (95 percent CI: 0.95, 1.47) for carriers of two variant *Gln* alleles (table 8; figures 4 and 5). No significant heterogeneity of individual study results was observed. Examination by geographic region produced summary odds ratios associated with the homozygous variant genotype of 1.00 (95 percent CI: 0.20, 5.18) for Asia, 1.08 (95 percent CI: 0.74, 1.57) for Europe, and 1.25 (95 percent CI: 1.03, 1.52) for the United States. There was no statistical evidence of publication bias in any analyses.

Because *XPD* helicase is a major protein in the repair pathway necessary for removal of tobacco-induced DNA lesions, *ERCC2/XPD* polymorphisms are presumed to affect smoking-related cancer risk by modulating the repair level. Therefore, the potential modifying effect of *XPD* genotype on the relation between lung cancer and tobacco smoking is of particular interest. Differences in association for *Asp312Asn* and *Lys751Gln* polymorphisms by level of smoking were investigated in some studies (tables 6 and 7); however, the statistical power to detect them was generally limited. A significant fourfold risk of lung cancer was found

among never smokers carrying the *Asn/Asn* genotype in comparison with persons with the *Asp/Asp* genotype (23); this excess risk was higher than that for smokers. Furthermore, among smokers, cancer risks associated with the *Asn/Asn* genotype decreased significantly as levels of tobacco exposure increased. Consistent with this finding, a twofold risk associated with the *Asn* allele was found among never smokers only in another study (12; table 6). Both of these studies reported the same tendency for the *Lys751Gln* polymorphism: a twofold risk among never smokers with the variant *Gln* allele as compared with persons who were homozygous for the *Lys* allele (table 7). Although there was no evidence of differences in risk in the remaining studies, these results are consistent with the hypothesis that the effect of genetic polymorphisms may be apparent only in the presence of lower levels or different classes of DNA damage than those caused by smoking (23).

In two studies (25, 52), the effect of *XPD* gene polymorphisms was also studied in combination with polymorphisms in the x-ray cross-complementing group 1 (*XRCC1*) gene. A significantly increased risk of lung cancer was found among persons with five or six variant alleles of the three *XPD* *Asp312Asn*, *XPD* *Lys751Gln*, and *XRCC1* *Arg399Gln* polymorphisms in comparison with persons with no variant alleles (52). Similarly, persons with allele variants for both the *XPD* *Lys751Gln* and *XRCC1* *Arg194Trp* polymorphisms

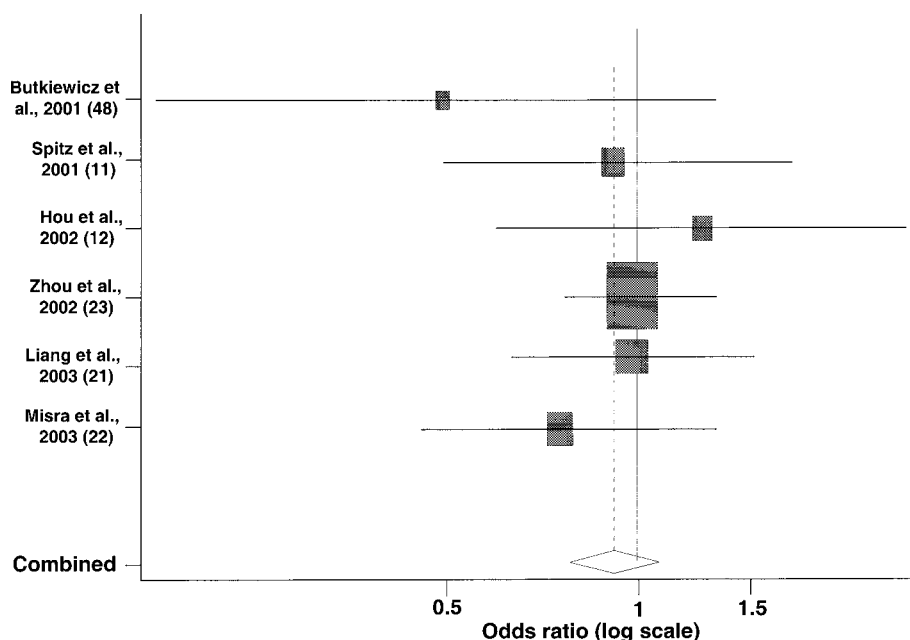


FIGURE 2. Odds ratios for the relation between the *Asp/Asn* genotype of the xeroderma pigmentosum group D *Asp312Asn* gene polymorphism (vs. the *Asp/Asp* genotype) and lung cancer risk. For each study, the odds ratio estimate is plotted with a box; the area of each box is inversely proportional to the estimated effect's variance in the study. Diamond, pooled odds ratio; horizontal lines, 95% confidence interval.

were found to be at higher risk of lung cancer than persons with only one of them (25).

Possible associations between polymorphic genes belonging to various metabolic pathways are being

researched. For example, Pastorelli et al. (53) reported significantly higher levels of benzo(*a*)pyrene diol epoxide-DNA adducts in lymphocytes from lung cancer patients only among persons exhibiting *GSTM1* deletion and having both

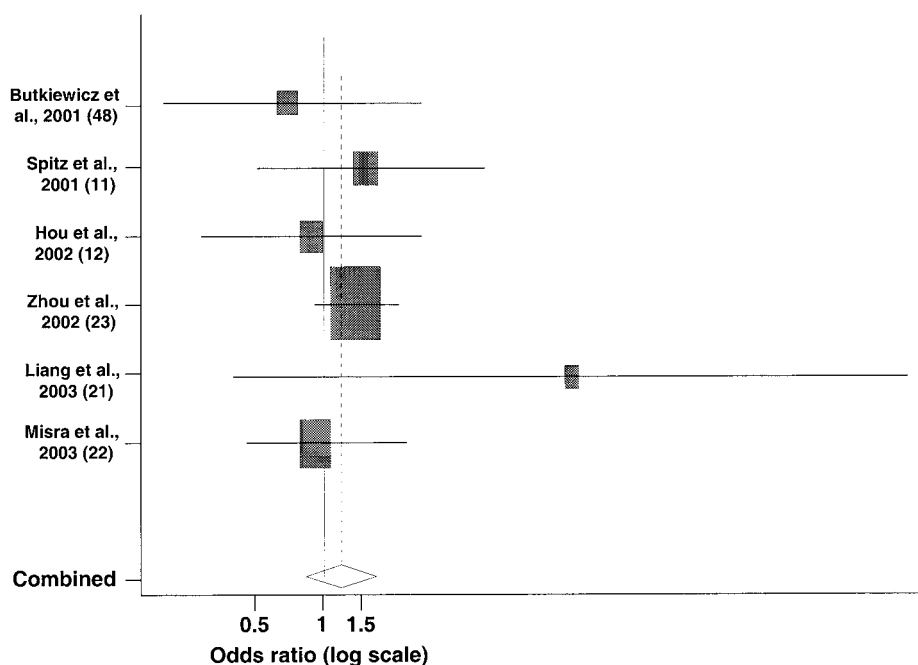


FIGURE 3. Odds ratios for the relation between the *Asn/Asn* genotype of the xeroderma pigmentosum group D *Asp312Asn* gene polymorphism (vs. the *Asp/Asp* genotype) and lung cancer risk. For each study, the odds ratio estimate is plotted with a box; the area of each box is inversely proportional to the estimated effect's variance in the study. Diamond, pooled odds ratio; horizontal lines, 95% confidence interval.

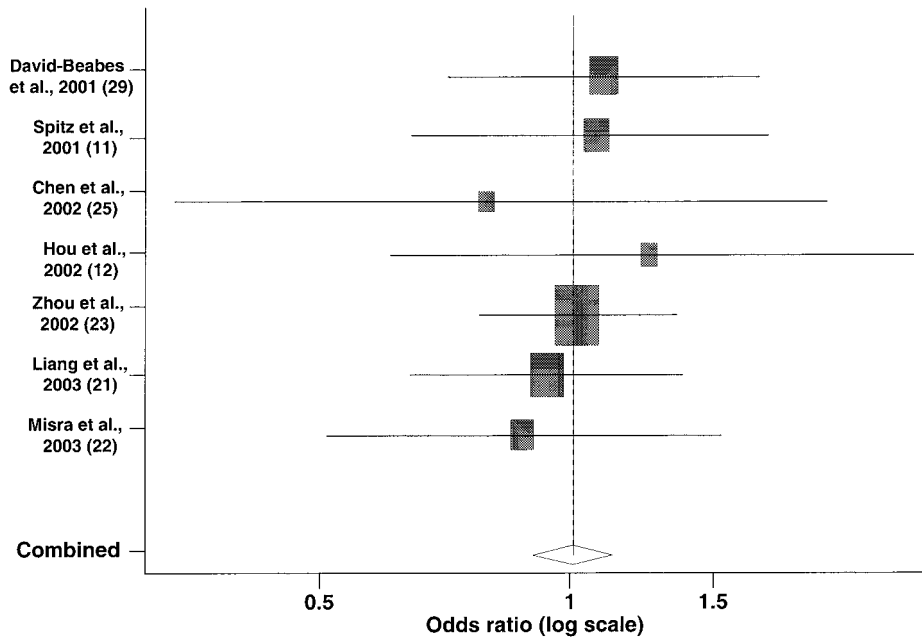


FIGURE 4. Odds ratios for the relation between the *Lys/Gln* genotype of the xeroderma pigmentosum group D *Lys751 Gln* gene polymorphism (vs. the *Lys/Lys* genotype) and lung cancer risk. For each study, the odds ratio estimate is plotted with a box; the area of each box is inversely proportional to the estimated effect's variance in the study. Diamond, pooled odds ratio; horizontal lines, 95% confidence interval.

XPD-312 and -751 wild-type alleles. This result does not correlate with the findings reviewed above. Because it seems to be true only in patients who are deficient in the *GSTM1* enzyme and therefore should have a greater number of DNA

adducts, it may be that the efficiency of DNA repair varies according to the absolute number of DNA lesions.

Several DNA repair pathways are involved in the maintenance of genetic stability. The most versatile and important

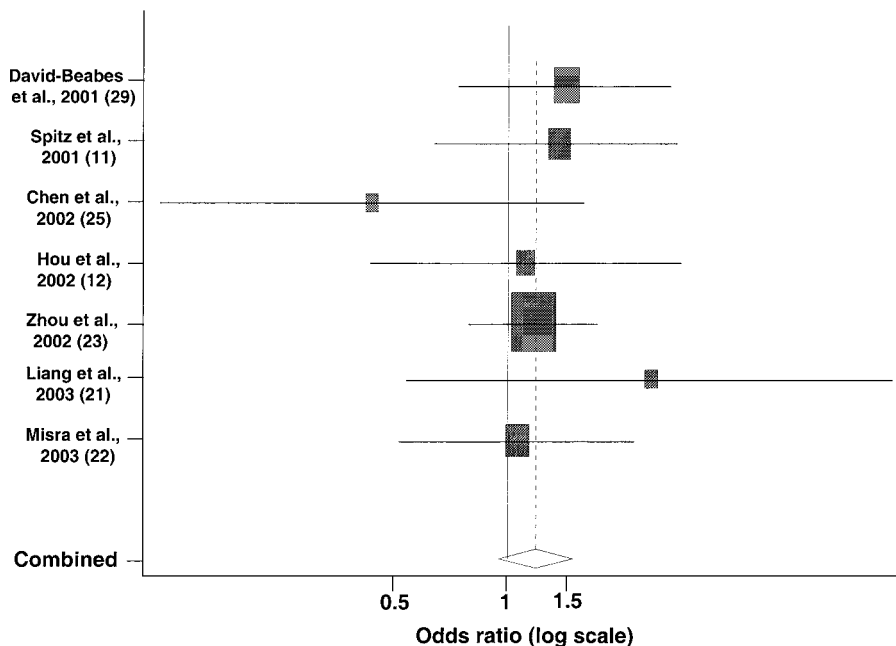


FIGURE 5. Odds ratios for the relation between the *Gln/Gln* genotype of the xeroderma pigmentosum group D *Lys751 Gln* gene polymorphism (vs. the *Lys/Lys* genotype) and lung cancer risk. For each study, the odds ratio estimate is plotted with a box; the area of each box is inversely proportional to the estimated effect's variance in the study. Diamond, pooled odds ratio; horizontal lines, 95% confidence interval.

one is the nucleotide excision repair pathway, which detects and removes bulky DNA adducts, including those induced by cigarette smoking (54). The existence of dramatic diseases associated with dysfunction of this pathway suggests that it may also be important in the general population. The base excision repair pathway involves removal of modified bases such as oxidized purines or pyrimidines that can also be produced following cigarette smoking. However, the redundancy of glycosylases and the absence of associated human diseases do not favor the possibility of a role for base excision repair in lung cancer. Mismatch repair removes unrepaired bases and partially recognizes bulky adducts. Because patients deficient in mismatch repair do not exhibit lung cancer, this pathway does not appear to be the prime candidate for study in relation to cigarette smoking. Finally, recombination pathways are able to remove or bypass bulky lesions, allowing the cells to tolerate them (55). The destruction of the genes governing these recombination pathways results in embryonic death (4), demonstrating that these pathways are absolutely necessary for life. Abnormal recombination may produce mutations or genetic instability leading eventually to cancer.

In analyzing these different DNA repair pathways, it is logical to prioritize the study of nucleotide excision repair, which is the major repair pathway for lesions produced by cigarette smoking. The XPD protein is a major player in this process, but because it also acts on RNA transcription, which is essential for cellular life, the reported polymorphisms may have little effect, if any, on biologic processes. Other genes that are not necessary for transcription, such as *XPA*, *XPC*, *XPE*, or *XPF*, may be revealed to be a better target for polymorphism analysis in this pathway.

If one excludes the study of nucleotide excision repair, the recombination pathways are probably a good target for further studies. Scientists would then have to choose either homologous or illegitimate recombination for analysis. Up to the present time, there have been no obvious data in the field to promote one of these two pathways.

In the case-control studies on lung cancer reviewed in this paper, investigators restricted their analysis to one or two *XPD* polymorphisms, and overall no evidence of associations was found. However, it may be only the joint effect of multiple polymorphisms within the gene that provides information about an association with lung cancer. Advances in identification of new variants and in high-throughput genotyping techniques will facilitate analysis of multiple polymorphisms within genes and multiple genes within the same pathway (56). Therefore, it is likely that the defining feature of future epidemiologic studies will be the simultaneous analysis of large numbers of polymorphisms in candidate genes in much larger samples of cases and controls (57, 58). It may be necessary to establish consortia of researchers investigating a particular cancer site to test the repeatability of findings. Furthermore, the effects of polymorphisms are perhaps best represented by their haplotypes (a set of closely linked polymorphisms inherited as a unit on the same chromosome). Recent haplotype-based methods have been proposed for evaluating associations with the disease phenotype; one method involves statistically inferring haplotypes from the genotype data of unrelated persons included in

case-control or cohort studies (59–61). Haplotype-based methods were not used in the studies we reviewed; however, it can be anticipated that in future association studies on cancer, the development of these and other computational approaches will facilitate the evaluation of haplotypic effects, either for selected polymorphisms physically close to each other or for multiple genes within the same DNA repair pathway.

INTERNET SITES

International Agency for Research on Cancer: <http://www.iarc.fr>

Online Mendelian Inheritance in Man (OMIM): <http://www.ncbi.nlm.nih.gov/Omim>

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